ON HAEMOGLOBIN METABOLISM IN MALARIAL FEVER

PART II. THE INFLUENCE OF QUININE

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In a previous paper[1] it was shown that the amount of haemolysis proceeding in the body can be measured to some extent by the total excretion of urobilin, the end product of the pigment of the blood: the intestinal elimination is more important than the urinary.

In malaria a high degree of haemolysis is followed by a high excretion of urobilin in the faeces, and sometimes also in the urine; in blackwater fever the amount of liberated haemoglobin excreted as this derivative is far larger than the amount passing unchanged through the kidneys.

In another communication[2] it was shown that a haemolytic principle can be demonstrated occasionally in malarial serum; this action is most likely to be shown by the serum of a benign tertian case drawn at the onset of a paroxysm.

Clinical evidence would seem to favour the view that quinine is a determining factor in many cases of blackwater fever, but Barrett and Yorke[3] have shown that this drug, in strengths comparable with those likely to be present in serum after its administration, has no haemolytic action *in vitro* on normal or malarial human corpuscles. Deeks and James,[4] in the Report on haemoglobinuric fever in the Canal Zone, give cases which demonstrate clearly that quinine does influence the production or action of haemolysins and cytolysins in malaria.

It is possible that, though quinine has no haemolytic action on red corpuscles *in vitro*, it may have such a power in the human body: this may be due to some reaction with the living bioplasm,

or to metabolites of quinine. Only about one-third to one-half of the amount of quinine ingested is excreted unchanged,[5] and the rest must be broken down in the body—many of the quinoline antipyretics proved so likely to cause haemolysis that their therapeutic use was abandoned.

Deeks and James have suggested that quinine may act as complement to haemolytic amboceptors produced by the body or by the malarial parasite.

We have undertaken a series of experiments to ascertain whether the administration of quinine to animals or man causes any increase in the excretion of urobilin, which would show that quinine has a haemolytic effect, direct or indirect.

EXPERIMENTS ON ANIMALS

The normal excretion of urobilin by rabbits was first determined; then the effects produced by injection of haemoglobin itself and various haemolytic drugs.

As was to be expected, an increased urobilin excretion was observed after injection of red corpuscles or haemoglobin and of haemolytics, including haemolytic antipyretics. Increase was also noted after the administration of quinine.

The accuracy of the figures, obtained by dilution methods, for the urobilin content of the faeces of these animals is somewhat unsatisfactory, owing to the interference of other pigments from the food and to the small increases obtained.

Normal average excretion of urobilin, 0·006 milligrammes per diem				Milligrammes
Total increase of excreted urobilin after injection of	1·836	grams of	haemoglobin	0·12
Total increase of excreted urobilin after administration of	0·64	,,	antipyrin	0·032
,, ,, ,,	3·0	,,	,,	0·123
,, ,, ,,	0·013	,,	mowrin	0·040
,, ,, ,,	0·05	,,	,,	0·018
,, ,, ,,	0·70	,,	quinoline	0·054
,, ,, ,,	0·04	,,	quinine	0·054
,, ,, ,,	1·65	,,	,,	0·086

Similar increases were obtained in dogs after administration of haemolytics, but only doubtful results were obtained after quinine and quinoline derivatives.

Normal average daily excretion of urobilin, 0·018 milligrammes						Milligrammes
Total increase from administration (intraperitoneal) of	...	...	...	10	grams of haemoglobin	0·160
Total increase after administration of	...			0·125	,, toluene-diamine	0·381
,,	,,	,,		0·250	,,	0·278
,,	,,	,,		0·400	,,	0·214
,,	,,	,,		0·250	,, quinine	0·006
,,	,,	,,		0·4	,, ,,	0·004
,,	,,	,,		1·0	,, thallin sulphate	0
,,	,,	,,		1·0	,, kairalin	0

It is interesting to note that the injection of toluene-diamine in dogs gives rise to increased urobilin excretion (without haemoglobinuria unless large doses are given); in a puppy we obtained jaundice with excretion of large amounts of bile in urine and faeces, and in cats the injection gave a slight increase of urobilin followed on the third day by severe haemoglobinuria.

In the puppy the dose was 0·4 gram, and the result may have been due to diarrhoea or to lack of the urobilin organisms in its intestinal flora. The difference between dogs and cats shows some difference in the mechanisms of blood destruction.[6]

The experiments on animals gave some support to the view that quinine might have a haemolytic action in the organism, and experiments were now made on man.

Man

1. In a hospital patient (non-malarial) the average excretion of urobilin was 50 mgms. The patient received on each of two successive days a dose of 2 grams (30 grains) of quinine. The average daily excretion in the subsequent period was 49 mgms. (It is probable that some stools were not saved.)

2. Healthy adult. Average daily excretion of urobilin 75 mgms.

Total increase of urobilin after 1 gram antipyrin per diem for two days, 72 mgms. The main increase was on the fifth day.

3. Healthy adult. Average daily excretion of urobilin 72 mgms.

(*a*) Quinine, 1·3 grams per diem for two days. Average daily excretion of urobilin 94 mgms. Total increase of urobilin 110 mgms. The main increase was on the fifth day. 110 mgms. urobilin equals 2·7 grams haemoglobin.

(b) Quinine, 2 grams on one day. Subsequent average excretion 82 mgms. Total increase of urobilin 50 mgms., = 1·2 grams haemoglobin.

In this individual quinine caused marked headache and indisposition on each occasion.

4. Healthy adult. Average urobilin excretion 40 mgms. per diem.

(*a*) Quinine, 3·3 grams on one day (marked indisposition). Average subsequent urobilin 53 mgms. per diem. Total increase of urobilin 59 mgms. = 1·47 grams haemoglobin.

(*b*) Quinine, 1 gram per diem for three days (no indisposition). Average subsequent urobilin = 42 mgms. per diem. Decrease of urobilin excretion.

5. Healthy adult. Average normal output of urobilin 113 mgms. per diem. 0·6 gram quinine per diem for three days (no indisposition). Subsequent average urobilin excretion 92 mgms. per diem. Decrease of urobilin.

6. Healthy adult. Average normal output of urobilin 112 mgms. per diem. One gram quinine daily for three days (slight symptoms of quininism). Average subsequent urobilin 107 mgms. per diem. No result from quinine.

7. Healthy adult. Average normal output of urobilin 86 mgms. per diem. One gram of quinine daily for three days (headache and malaise). Average subsequent urobilin 105 mgms. per diem (maxima on fourth and seventh days). Total urobilin increase 152 mgms., equivalent to 3·6 grams of haemoglobin.

8. Healthy adult. Average normal output of urobilin 175 mgms. Two grams of quinine on one day (marked headache and malaise). Average subsequent urobilin 205 mgms. Total urobilin increase 270 mgms. = 6·4 grams haemoglobin.

These experiments on the whole support the results obtained

from experiments on animals, and it appears probable that administration of quinine may give rise to destruction of red corpuscles. The increase is more likely to occur when symptoms of quininism are produced.

The experiments require to be repeated on a larger scale, preferably where both malarial and non-malarial individuals are regularly taking prophylactic doses of quinine. The claims of other work have prevented us making many observations.

To be conclusive, the subjects of experiment should be on a constant diet with little meat (as foreign blood pigment from the diet exercises some influence); the experiments require to continue for seven to ten days after the administration of quinine has ceased.

Graham[7] has shown by photographic methods a regular increase of urobilin in the urine after prophylactic doses of quinine. His experiments did not cover the important faecal channel of elimination, but the regularity of the increase is very marked, and faecal determinations would probably have confirmed the urinary ones.

CONCLUSIONS

1. Increased excretion of urobilin may occur after the administration of quinine in doses of ten to thirty grains a day. A similar result follows injection of blood pigment or haemolytic drugs.

2. Quinine probably possesses the power of determining haemolysis in the body, though the exact mechanism of its action must be further investigated.

3. Individual or pathological idiosyncrasy may exaggerate this action and so account for the influence of quinine in blackwater fever.

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REFERENCES

1. Annals of Trop. Med. and Parasit., Vol. IV, 1910.
2. Annals of Trop. Med. and Parasit., Vol. VI, 1912.
3. Annals of Trop. Med. and Parasit., Vol. III, 1909.
4. 'Report on Haemoglobinuric Fever in the Canal Zone.' Isthmian Canal Commission, p. 62 *et seq.*, 1911.
5. Arch. f. Schiffs und Tropenhygiene, Bd. XI, 1907.
6. Afannassiew. Virch. Archiv., Vol. XCVIII, 1884.
7. Graham. Annals of Trop. Med. and Parasit., Vol. V, 1911.